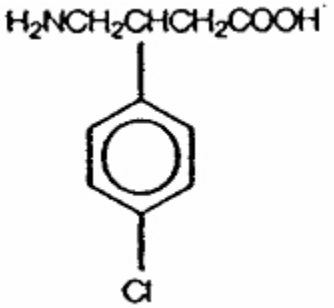
KEMSTRO - baclofen tablet, orally disintegrating
Schwarz Pharma

DESCRIPTION

KEMSTRO™ (baclofen orally disintegrating tablets) is a muscle relaxant and antispastic. Baclofen USP is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform. Its chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid. The molecular weight of baclofen is 213.66 and the empirical formula is $C_{10}H_{12}ClNO_2$. The structural formula is represented below:



KEMSTRO™ is available as 10 mg and 20 mg orally disintegrating tablets. Each orally disintegrating tablet also contains as inactive ingredients: aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor and povidone.

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

Pharmacokinetics

Absorption

Baclofen is rapidly and extensively absorbed. Absorption may be dose-dependent, being reduced with increasing doses. KEMSTRO™ given with or without water is bioequivalent to the baclofen conventional tablet. Thus KEMSTRO™ can be placed on the tongue until it disintegrates and then be swallowed with or without water. Following a single 20 mg oral dose of KEMSTRO™, the peak plasma concentration was reached about 1½ hours after administration.

Distribution

The apparent volume of distribution is 59 liters. Baclofen does not readily cross the blood-brain barrier. Plasma protein binding is approximately 30%.

Metabolism

In a study using radiolabeled baclofen, approximately 85% of the dose was excreted unchanged in the urine and feces. About 15% of the dose was metabolized, primarily by deamination. The γ-hydroxy metabolite, 3-(*p*-chlorophenyl)-4-hydroxybutyric acid, is formed after deamination of baclofen.

Excretion

Baclofen is rapidly and extensively eliminated. There is a relatively large intersubject variation in elimination. Baclofen is excreted primarily by the kidney as unchanged drug; 70 - 80% of a dose appears in the urine as unchanged drug. The remainder is excreted as unchanged drug in the feces or as metabolites in the urine and feces. Excretion is complete within 72 hours after administration. The elimination half-life of KEMSTRO™ is approximately 5½ hours. Total systemic clearance is 180 mL/min and renal clearance is 103 mL/min.

Special Populations

Elderly

The pharmacokinetics of baclofen tablets were evaluated in elderly patients (69-81 years) and in healthy younger subjects (23-53 years) after a single 10 mg dose. The C_{max} was lower (119 ng/mL vs. 178 ng/mL) and the T_{max} was longer (3 hours vs. 1 hour) in the elderly patients compared to the younger subjects. The AUCs were similar in the two groups. In this study, the elimination half-life was slightly prolonged in the elderly patients compared to the younger subjects, 4.43 hours vs. 3.75 hours, respectively.

INDICATIONS AND USAGE

KEMSTRO™ is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.
Patients should have reversible spasticity so that treatment with KEMSTRO™ will aid in restoring residual function.
KEMSTRO™ may also be of some value in patients with spinal cord injuries and other spinal cord diseases.
KEMSTRO™ is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.
The efficacy of KEMSTRO™ in stroke, cerebral palsy, and Parkinson's disease has not been established and, therefore, it is not recommended for these conditions.

CONTRAINDICATIONS

KEMSTRO™ is contraindicated in patients who are hypersensitive to any component of this product.

WARNING

Abrupt Drug Withdrawal

Hallucinations and seizures have occurred on abrupt withdrawal of baclofen. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued.

Impaired Renal Function

Because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function.

Stroke

Baclofen has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.

PRECAUTIONS

General

Baclofen should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.
In patients with epilepsy, the clinical state and electroencephalogram should be monitored at regular intervals, since deterioration in seizure control and EEG have been reported occasionally in patients taking baclofen.

Information for patients

Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of baclofen may be additive to those of alcohol and other CNS depressants.

Phenylketonurics

Phenylketonuric patients should be informed that KEMSTRO™ contains phenylalanine
3.9 mg per 10 mg orally disintegrating tablet and 7.9 mg per 20 mg orally disintegrating tablet.

Interactions

Drug interactions
The central nervous system depressant effects of baclofen may be additive to those of alcohol and other CNS depressants.

Carcinogenesis, mutagenesis, impairment of fertility

A dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed in female rats treated chronically with baclofen.
Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients that were treated with baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

Pregnancy

Pregnancy Category C. Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended for human use, at a dose which caused significant reductions in food intake and weight gain in dams. This abnormality was not seen in mice or rabbits. There was also an increased incidence of incomplete sternebral ossification in fetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in fetuses of rabbits given approximately 7 times the maximum recommended human dose. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 or 34 times the human daily dose. There are no adequate and

well-controlled studies in pregnant women. KEMSTRO™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KEMSTRO™ is administered to a nursing woman.

Pediatric use
Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric use
Clinical studies of baclofen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of KEMSTRO™ and observed closely.

ADVERSE REACTIONS
The most common adverse reaction during treatment with baclofen is transient drowsiness (10-63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen tablets compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (5-15%) and fatigue (2-4%). Others reported:
Neuropsychiatric: Confusion (1-11%), headache (4-8%), insomnia (2-7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.
Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.
Gastrointestinal: Nausea (4-12%), constipation (2-6%); and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.
Genitourinary: Urinary frequency (2-6%); and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.
Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.
Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.
The adverse experience profile seen with KEMSTRO™ was similar to that seen with baclofen tablets.

DRUG ABUSE AND DEPENDENCE

Overdosage

Signs and Symptoms
Vomiting, muscular hypotonia, drowsiness, accommodation disorders, coma, respiratory depression, and seizures.

Treatment
In the alert patient, empty the stomach promptly by induced emesis followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Maintain adequate respiratory exchange, do not use respiratory stimulants. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentration of baclofen.

DOSAGE AND ADMINISTRATION
The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).
The following dosage titration schedule is suggested:
5 mg three times a day for 3 days
10 mg three times a day for 3 days
15 mg three times a day for 3 days
20 mg three times a day for 3 days
Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg four times a day).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see WARNINGS, Abrupt Drug Withdrawal).

Administration
Using dry hands, the patient should be instructed to place the tablet on the tongue, where it will disintegrate and can then be swallowed with or without water.

Patients with Renal Impairment
Because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function.

HOW SUPPLIED
KEMSTRO™ (baclofen orally disintegrating tablets) 10 mg are white, round, orange-flavored, scored and engraved “10” on the unscored side and “SP” above and “351” below the score on the other side. They are supplied as follows:
Bottles of 100NDC 0091-3351-01
KEMSTRO™ (baclofen orally disintegrating tablets) 20 mg are white, round, orange-flavored, scored and engraved “20” on the unscored side and “SP” above and “352” below the score on the other side. They are supplied as follows:
Bottles of 100NDC 0091-3352-01
Dispense in a tight container as defined in the USP/NF with a child-resistant closure.
Store at controlled room temperature 20º- 25º (68º- 77º); excursions permitted between
15º- 30º (59º- 86º). Protect from moisture.
Manufactured for:
Schwarz Pharma

MILWAUKEE, WI 53201, USA
By:
CIMA LABS INC.®

Eden Prairie, MN 55344, USA
KEMSTRO™ uses CIMA U.S. Patent Nos. 6,024,981 and 6,221,392.
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